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Ambient Water Quality Criteria Hexachlorobutadiene

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HEXACHLOROBUTADIENE

Ambient Water Quality Criteria

Criteria and Standards Division
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U.S. Environmental Protection Agency
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CRITERION DOCUMENT

HEXACHLOROBUTADIENE

Criteria

Aquatic Life

For freshwater aquatic life, no criterion for hexachlorobutadiene can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

For saltwater aquatic life, no criterion for hexachlorobutadiene can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to hexachlorobutadiene through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of hexachlorobutadiene estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 0.77 µg/l, 0.077 µg/l, and 0.0077 µg/l, respectively.

BIBLIOGRAPHIC INFORMATION

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Ambient Water Quality Criteria: Hexachlorobutadiene.

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for hexachlorobutadiene. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in its, ...

KEYWORDS: *Water quality, *Toxicology, *Chlorobutadienes, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances, *Butadiene/hexachloro.

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Introduction

Hexachlorobutadiene (HCBD) is not produced in the United States but is a significant by-product of the manufacture of chlorinated hydrocarbons such as tetrachloroethylene, trichloroethylene, and carbon tetrachloride. Secondary production estimates range from 7.3 to 14.5 million pounds per year (U.S. EPA, 1975a). In 1974, approximately 0.5 million pounds were imported into the U.S. (U.S. EPA, 1975a).

HCBD is used as a solvent for many organic substances; its low vapor pressure gives it a distinct advantage over some other chlorohydrocarbons for this purpose. The largest domestic users of HCBD are chlorine producers, which use it to recover chlorine from "snift" gas which is cleaned by passage through HCBD. Other applications of HCBD include its use as an intermediate in the manufacture of rubber compounds and lubricants and as a fluid for gyroscopes (U.S. EPA, 1975a).

HCBD, a colorless liquid with a faint turpentine-like odor, has a water solubility of only 5 µg/ml at 20 degrees C. It has a melting point of -21 degrees C and a vapor pressure of 0.15 mm Hg (McBee and Hatton, 1949; McConnell, et al. 1975).

Environmental contamination by HCBD results primarily during the disposal of wastes containing HCBD from chlorinated hydrocarbon industries (U.S. EPA, 1976). Disposal methods include landfill, high temperature incineration, deep-well injection, and lagoon storage (U.S. EPA, 1975a). HCBD has been detected in a limited number of surface waters that serve as U.S. drinking water supplies (U.S. EPA, 1975b).

Highest levels have been measured in air, water, soil, and sediment in the vicinity of chlorinated hydrocarbon industries (Laseter, et al. 1976).

HCBD appears to be rapidly adsorbed to soil and sediment from contaminated water and is known to concentrate in sediment from water by a factor of 100 (Leeuwangh, et al. 1975).

The presence of HCBD in aquatic life ranges from relatively high levels in freshwater organisms from industrially polluted inland waters (Laseter, et al. 1976) to considerably less in organisms from marine environments (Pearson and McConnell, 1975). Studies of the toxicity of HCBD to aquatic organisms indicate that levels below one part per million are biologically significant as indicated by reported LC50 values, (Leeuwangh, et al. 1975; Pearson and McConnell, 1975; Laseter, et al. 1976; Laska, et al. 1978).

Experimental evidence in non-human mammals shows that HCBD is fetotoxic, neurotoxic, nephrotoxic and is carcinogenic at severely toxic levels (Poteryaeva, 1966, 1973; Murzakeav, 1967; Kociba, et al. 1977; Schwetz, et al. 1977; Gage, 1970).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Available data for hexachlorobutadiene indicate that it is acutely toxic to freshwater aquatic life in the range of 90 to 210 µg/l. A physiological change in fish blood occurred at much lower concentrations.

Acute Toxicity

Goldfish have been tested (Leeuwangh, et al. 1975) and the 96-hour LC50, after adjustment for test methods as directed by the Guidelines, is 64 µg/l (Table 1). After division by the sensitivity factor (3.9), a Final Fish Acute Value of 16 µg/l is obtained.

A snail and a sowbug have been exposed to hexachlorobutadiene and the adjusted 96-hour LC50 values are 231 and 143 µg/l, respectively (Table 2). These data result in a Final Invertebrate Acute Value of 8.7 µg/l which becomes the Final Acute Value since it is lower than the equivalent value for fish.

Chronic Toxicity

No chronic tests have been conducted with freshwater species.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Plant Effects

No freshwater algal or vascular species have been tested.

Residues

Bioconcentration factors have been determined for goldfish (Leeuwangh, et al. 1975) and range from 920 to 2,300 (Table 3). Laseter, et al. (1976) obtained bioconcentration factors for an alga, crayfish and largemouth bass of 160, 60, and 29, respectively.

Miscellaneous

Laska, et al. (1978) exposed largemouth bass to concentrations of hexachlorobutadiene between 3.43 and 31.95 µg/l for 10 days and observed elevated blood corticosteroid levels. These changes occurred at concentrations as low as the Final Acute Value and such effects might influence chronic toxicity.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 16 µg/l

Final Invertebrate Acute Value = 8.7 µg/l

Final Acute Value = 8.7 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 3.8 µg/l

No freshwater criterion can be derived for hexachlorobutadiene using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 1. Freshwater fish acute values for hexachlorobutadiene (Leeuwangh, et al. 1975)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Goldfish, Carassius auratus	R	M	96	90	64

* R = renewal

** M = measured

Geometric mean of adjusted values = 64 µg/l $\frac{64}{3.9}$ = 16 µg/l

Table 2. Freshwater invertebrate acute values for hexachlorobutadiene (Leeuwangh, et al. 1975)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Snail, Lymnaea stagnalis	R	M	96	210	231
Sowbug, Asellus aquaticus	R	M	96	130	143

* R = renewal

** M = measured

Geometric mean of adjusted values = 182 µg/l $\frac{182}{21}$ = 8.7 µg/l

Table 3. Freshwater residues for hexachlorobutadiene

Organism	Bioconcentration Factor	Time (days)	Reference
Crayfish, *Procambarus clarki*	60	10	Laseter, et al. 1976
Goldfish, *Carassius auratus*	920-2,300	49	Leeuwangh, et al. 1975
Largemouth bass, *Micropterus salmoides*	29	10	Laseter, et al. 1976
Alga, *Oedogonium cardiacum*	160	7	Laseter, et al. 1976

Table 4. Other freshwater data for hexachlorobutadiene (Laska, et al. 1978)

Organism	Test Duration	Effect	Result (ug/l)
Largemouth bass, *Micropterus salmoides*	10 days	Elevated blood corticosteroid levels	3.43 31.95

SALTWATER ORGANISMS

Introduction

No data on the effects of hexachlorobutadiene on saltwater aquatic life are available.

CRITERION FORMULATION

No saltwater criterion can be derived for hexachlorobutadiene using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

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Mammalian Toxicology and Human Health Effects

I. Exposure

A. Ingestion

1. Water

In 1974, the U. S. Environmental Protection Agency undertook a survey of finished water from three New Orleans area water plants (Keith, et al. 1976). Immediately upstream on the Mississippi River from New Orleans are numerous petrochemical and chemical plants including some producing chlorohydrocarbon compounds. The concentrations of HCBD found ranged from 0.07 to 0.7 µg/l HCBD for the three test sites.

In 1975, a followup study conducted by EPA included 10 cities (U.S. EPA, 1975). HCBD was identified in one of the drinking water supplies surveyed in this group and the concentration was less than 0.01 µg/l. HCBD has been found in water samples taken from inland sites bordering the lower Mississippi River (Laseter, et al. 1976). In this study, a landfill pond near an industrial source was found during one month of the survey to contain 4.49 µg/l and the corresponding value for the surrounding mud was 920 µg/kg (corrected to dry weight). Effluents from industrial plants suspected of being sources of HCBD contained concentrations ranging from 0.04 to 240 µg/l (Li, 1976).

The conclusions regarding HCBD contamination of drinking water supplies are: (1) HCBD contamination of U.S. finished drinking water supplies does not appear to be a widespread problem; (2) the problem is localized in areas with raw water sources near industrial plants producing HCBD; (3) the physical and chemical characteristics of HCBD favor rapid extraction of HCBD from contaminated water into the surrounding sediment and mud (Laseter, et al. 1976).

2. Food

Since the water, soil, and air surrounding certain chlorohydrocarbon plants have been shown to be contaminated with HCBD (Li, 1976), food produced in the vicinity of these plants is most likely to contain residual levels of HCBD. A survey of foodstuffs within a 25-mile radius of tetrachloroethylene and trichloroethylene plants was made. Milk, eggs, and vegetable samples did not contain measurable levels of HCBD. Freshwater fish caught in the lower Mississippi river contained HCBD residues in a range of 0.01 to 1.2 mg/kg.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 2,300 was obtained for hexachlorobutadiene using goldfish containing about 6 percent lipids (Leeuwangh, et al. 1975). Lower BCF values were obtained at exposure concentrations that caused loss of equilibrium. The data of Laseter, et al. (1976), were not used since no recoveries were reported and the results showed inconsistencies and great variability. An adjustment factor of 2.3/6.0 = 0.38 can be used to adjust the measured BCF from the 6.0 percent lipids of the goldfish to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for hexachlorobutadiene and the edible portion of all aquatic organisms consumed by Americans is calculated to be 2,300 x 0.38 = 870.

Studies on HCBD contamination of food supplies have been reported from several foreign countries. In England, McConnell, et al. (1975) detected HCBD in fresh milk (0.08 µg/kg), imported grapes (3.7 µg/kg), and in tomatoes (0.8 µg/kg) grown on a reclaimed lagoon which was once used as a disposal area for a chemical plant. In Germany, Kotzias, et al. (1975) found 4 µg/kg HCBD in evaporated milk, 42 µg/kg in egg yolk, 33 µg/kg in vegetable oil margarine, and 39 and 2 µg/kg in chicken grain feed and laying rations, respectively.

B. Inhalation

The air in the vicinity of plants producing tetrachloroethylene, tri-

chloroethylene, and carbon tetrachloride has been shown to be contaminated with HCBD (Li, et al. 1976). A value as high as 460 $\mu g/m^3$ has been detected in one instance, but generally, the levels of HCBD detected in air surrounding these chlorohydrocarbon plants were less than 5 $\mu g/m^3$. There are uncertainties concerning the atmospheric fate of HCBD, but Pearson and McConnell (1975) reported a tropospheric half-life of approximately 1 week for HCBD. Unless someone lives or works in the vicinity of a chemical plant producing HCBD as a major byproduct, exposure to HCBD through inhalation would not seem to pose a problem.

II. Pharmacokinetics

Jacobs, et al. (1974) gave oral doses of a mixture of seven chlorinated hydrocarbons (2 mg/kg/component and 4 mg/kg/component) to rats daily for up to 12 weeks. Rats sacrificed at 4, 8, and 12 weeks had roughly 7 mg/kg or less HCBD at both dose levels accumulated in fatty tissue taken from the inner genital and kidney regions. The quantity found in the liver, heart, kidney, and blood was less than that found in the fatty tissue. These results showed that HCBD did not have a strong tendency to accumulate in fatty tissue of selected organs if administered in a mixture with other chlorinated hydrocarbons, some of which were aromatic and accumulated significantly in the fat.

III. Effects

In 1971, Gehring and MacDougall (1971) completed a review of the toxic properties of HCBD. These authors concluded that the data available at that time did not allow for a critical evaluation of any potential hazard

associated with long-term, repeated low level exposure to HCBD. Since then, several excellent studies have been published on the effects in rats of repeated, low level exposure to HCBD. Kociba, et al. (1977) conducted a 2-year study during which rats were given doses of 0.2, 2.0, and 20 mg/kg/day HCBD in their diet and found HCBD induced renal neoplasms at the highest dose level. Schwetz, et al. (1977), working in the same laboratory, found that these same dosage levels had virtually no effect on the reproduction and offspring of rats. Only a slight decrease in body weight of weanlings at 21 days of age was observed at the highest dose level.

A. Acute, Subacute, and Chronic Toxicity

A table summarizing the acute toxicity data on HCBD which was published prior to 1971 was prepared by Gehring and MacDougall (1971) in their review and is reproduced in this document as Table 2-A. Pre-1971 acute toxicity data not included in their table and acute data published since are summarized in Table 2-B. Oral LD_{50}'s range from a low of 46 mg/kg in the female weanling rat to a high of 580 mg/kg in the adult male rat indicating that HCBD has a relatively high acute toxicity by the oral route and some sex and age differentiation exists. The few data on acute dermal and inhalation exposure to HCBD show that HCBD is hazardous when encountered by these routes.

The subacute and chronic toxicity data are summarized in Table 3. A column has been included in this table and in Table 2-B giving the purity of the HCBD reagent used in each respective study. This piece of information is essential in making a final judgment on the usefulness of published data for assessing the toxicity of a particular substance. Unfortunately, no indica-

TABLE 2-A* - Acute toxicity of hexachlorobutadiene

Reference	Route	Species	HCBD Purity	No. of Animals	Solvent	Dose	Exposure Time	LD_{50} mg/kg	Observations
1	Oral	Rat						270	
2								350	
3				6	Corn oil, 3%			200	
2		G. Pig						90	
2		Mice						87	
1								116	
						500 mg			Some deaths
4	Dermal	G. Pig				126 mg/kg	24 hr		All died
3		Rabbits		4	Propylene glycol	126 mg/kg	7 hr		50% mortality
3				2		126 mg/kg	4 hr		No deaths
3				2		63 mg/kg	24 hr		No deaths
3				2					
						500 ppm	4 hr		All died
3	Inhalation	Rats		3		200 ppm	4 hr		Two deaths
3				3		200 ppm	2 hr		One death
3				3		34 ppm	3.5 hr		No deaths
5				6		161 ppm	0.83 hr		No deaths
5				5		274 ppm	3.5 hr		All died
5				6		314 ppm	0.88 hr		One death
5				6		133 ppm	7 hr		All died
3				6		34 ppm	3.5 hr		One death
5		G. Pig		2		161 ppm	0.88 hr		One death
5				2		27.5 ppm	7 hr		All died
3				4		34 ppm	3.5 hr		All died
3		Cats		2		161 ppm	0.88 hr		All died
5				2					

* Reproduced from Gehring & MacDougall, 1971.
Blank means no data available.

1 Gulko, et al. 1964.
2 Murzakaev, 1963.
3 Unpublished data, The Dow Chemical Company
4 Murzakaev, 1966.
5 Treon, & Edwards, 1948.

TABLE 2-8 - Continuation of Acute Toxicity Data on Hexachlorobutadiene

Reference	Route	Species	HCBD Purity	No. of Animals	Solvent	Dose	Exposure Time	LD_{50} mg/kg	Observations
1	Oral	Rat (F)	99%					200-400	
1		Rat (M)	99%					580	
1		Rat (F)	99%					65	21 days old
1		Rat (M)	99%					64	21 days old
2		Rat (M)						250	Caused hepatic and renal disorders, and appeared to affect central nervous of mice
2		Mice (M)						80	
3		Rat (M)		5		529 mg/kg*	Single	298*	All died in 5 days
3		Rat (M)		5		16 mg/kg*	Single		No deaths
3		Rat (M)						216	
2	IP	Rat (M)						105	
2	IP	Mice (M)						76	
4		Mice (M)				6800 ppm ✓			Lt50 275 min.
3	Inhalation	Rat				6800 ppm ✓			Lt50 310 min.
		Mice				6800 ppm ✓			Lt50 200 min.
		Guinea pig				5290 mg/kg*	Single		All died
3	Dermal -	Rabbit		5				2981	
3		Rabbit				2000 mg/kg	Single		All in three died
5		Rabbit				5000 mg/kg	Single		Absolute lethal dose
5		Rat						4330	
5		Rat							

* Converted from ul/kg using density of 1.675 mg/ul

✓ Aerosol dose; estimated concentration

Blank areas mean no data available

1. Schwetz, et al 1977.
2. Gradiski, 1975.
3. Hazelton Labs. 1978.
4. Gradiski, 1974.
5. Chernokan, 1970.

TABLE 3 - Subacute and chronic toxicity of hexachlorobutadiene

Ref.	Route	Species	No. of Animals	% HCBD Purity	Dose	Duration	Observations
1	Oral (diet)	Rat (M)	39	99	20 mg/kg/day	22 mo	Renal tubular neoplasms; metastasis to the lung
		Rat (F)	40	99	20 mg/kg/day	24 mo	
		Rat (M)	40	99	2 mg/kg/day	22 mo	Increased urinary coproporphyrin, increase in renal tubular epithelial hyperplasia
		Rat (F)	40	99	2 mg/kg/day	24 mo	
		Rat (M)	40	99	0.2 mg/kg/day	22 mo	No effects
		Rat (F)	40	99	0.2 mg/kg/day	24 mo	
2	Oral (diet)	Rat (F)	4	99	1 mg/kg/day	30 days	No effects
		Rat (F)	4	99	3 mg/kg/day	30 days	Marginal change in kidney/body weight ratio; no pathologic alterations
		Rat (F)	4	99	10 mg/kg/day	30 days	Decreased body weight gain; no pathologic alterations
		Rat (F)	4	99	30 mg/kg/day	30 days	Renal tubular epithelial degeneration, individual cell necrosis and regeneration, decreased body weight gain; increase in mean kidney:body weight ratio; increase in hemoglobin concentration
		Rat (F)	4	99	65 mg/kg/day	30 days	
		Rat (F)	4	99	100 mg/kg/day	30 days	
3	Oral (diet)	Rat (M)	12	99	0.2 mg/kg/day	148 days	No effects among adults or neonates
		Rat (F)	24	99	0.2 mg/kg/day	148 days	No effects among adults or neonates
		Rat (M)	10	99	2.0 mg/kg/day	148 days	Kidney "roughened," mottled cortex; other kidney changes which normally occur appeared to be accentuated
		Rat (F)	20	99	2.0 mg/kg/day	148 days	Accentuation of normal kidney changes; one had renal lesions identical to those on 20 mg/kg/day; no effects on neonates
		Rat (M)	12	99	20 mg/kg/day	148 days	Change in kidney body weight ratio; kidney roughened with mottled cortex; renal tubular dilation and hypertrophy with foci of renal tubular epithelial degeration and regeneration
		Rat (F)	24	99	20 mg/kg/day	148 days	Renal tubular dilation and hypertrophy with foci of renal tubular epithelial degeneration and regeneration; decreased value of body weight and heart, increased values for relative weight of brain and kidney; slight decrease in body weight of neonates at time of weaning.
4	Oral	Rat			0.0005 mg/kg/day	6 mo	Was at threshold level with respect to toxicity
		Rat			0.004 mg/kg/day	4 mo	Weakly toxic
		Rat			0.02 mg/kg/day	2 mo	Highly toxic

TABLE 3 - (Continued)

Ref.	Route	Species	No. of Animals	% HCBD Purity	Dose	Duration	Observations
5	Oral	Rat			8.4 mg/kg 100 mg/kg		Severe necrotic nephrosis, as well as abnormal changes in the brain, liver, and other internal organs
6	Oral	Guinea Pig			60 mg/kg 90 mg/kg	Single	Decompensatory acidosis most significant at 5 days. Those surviving 15 days, the blood indicators of acid-base equilibrium were normalized.
7,8	Oral	Dog			1 mg/kg/day	6 mos	Administered to puppies from birth to 6 mos. Increased secretion of total N containing compounds. Increaseed vol. and total acidity of the gastric juice.
9	Oral	Dog			0.05 mg/kg/day	45 days	Administered 1.5 to 3 months postnatal; increased total vol., acidity, and amount of HCl and chloride secreted by the stomach
10	Oral	Guinea Pig			0.004-2 mg/kg/day	7 mos	2 mg dose caused a decrease in -SH group conc. in blood plasma without change in blood protein plasma spectrum
11	Parenteral	Rat (F) Rat (F) Rat (F)	5 5 5		0.004 mg/kg 0.04 mg/kg 7.0 mg/kg	6 mos 6 mos 6 mos	No effect on rate of forming positive conditioned reflexes. Acceleration of the forming of differentiation was noted. Decrease in the SH content of the cerebral cortex homogenate; disturbed ability of the animal to form conditioned reflex connections; Exhibited morphological changes in the liver, kidneys, and cardiac muscle in the form of parenchymatous dystrophy
12	IP	Mice	20		4 mg/kg 8 mg/kg	3 wk to total of 52 mg 3 wk to total of 96 mg	No statistically significant increase in the production of adenomas
13	Subcutaneous	Rat (F)			20 mg/kg	Single	Administered to pregnant mice, caused disturbances of motor coordination; weight loss, lymphocytosis, neutropenia, mylecytosis, death occurred in 100% of the offspring within 3 months after injection.
14	Inhalation	Rat Mice			24 mg/m^3-air 24 mg/m^3-air	7 mos 7 mos	Caused no alterations
15	Inhalation	Rat			0.01 mg/m^3-air	6 mos (5 hr daily)	No effects observed

TABLE 3 - (Continued)

Ref.	Route	Species	No. of Animals	% HCBD Purity	Dose	Duration	Observations
16	Inhalation	Rat (4 M)	4		25 ppm	15 daily	Caused respiratory difficulty; decreased weight gain and
		Rat (4 F)	4		25 ppm	for 6 hrs	pathologic injury to the tubular epithelium of the kidneys
		Rat (4 M)	4		100 ppm	12 daily	
		Rat (4 F)	4		100 ppm	for 6 hrs	Severe toxicity including death
		Rat (4 M)	4		10 or 5 ppm	15 daily	
		Rat (4 F)	4		10 or 5 ppm	for 6 hrs	Caused no toxicity except for retarded weight gain in females at 10 ppm
17	Cutaneous & ocular	Rat				Single	Irritant
18	Dermal	Rat			1,675 mg/kg*	24 hrs	Mild to moderate erythema
19	Inhalation, oral, and topical	Rat, mice, guinea pig & cats					Acute and chronic toxicity experiments performed on large groups of rats, mice, guinea pigs, and cats. Leucocytosis, lymphocytosis, along with decreased erythrocytic osmosis and resistance were ascertained in terms of hematology; immunological depression and decreased antibody formation observed
20					8.4 mg/kg	Single	Largest concentration of HCBD found in proximal sections
					10 mg/kg	Single	of the nephrons: dystropic changes in kidneys caused by 8.4 mg/kg; necrosis at 10 mg/kg

* Converted from ul/kg using density of 1.675 mg/ul. Blank areas mean no data available.

TABLE 3 - (Continued)

References

1. Kociba, et al. 1977
2. Kociba, et al. 1971
3. Schwetz, et al. 1977
4. Poteryaeva, 1973
5. Dimitrienko, & Vasilos, 1972
6. Popovich, 1975
7. Boranova, 1974a
8. Boranova, 1974b
9. Kravitskaya, & Boranova, 1974
10. Murzakaev, 1965
11. Murzakaev, 1967
12. Theiss, et al. 1977
13. Poteryaeva, 1966
14. Gulko, et al. 1964
15. Poteryaeva, 1972
16. Gage, 1970
17. Duprat, et al. 1976
18. Human, & Lawless, 1975
19. Poteryaeva, 1971
20. Shroit, et al. 1972

tion of the purity of the reagent has been given in many of the publications on HCBD toxicity.

A considerable portion of the literature on HCBD toxicity is reported in Russian. For the majority of these publications, only an abstract was available, or there was not sufficient time to obtain complete translation of the full article. All publications on HCBD toxicity reported in the literature are given in the tables. The Chemical Abstracts Service abstract number is given along with the reference for each Russian publication. Those publications for which translations were available are labeled so in the references. Because details of the experimental procedures and results were not included in many of the abstracts of the Russian articles (and often not in the full translations), only a limited reference to Russian literature is made in the main body of this document. None of the Russian articles attributed carcinogenic properties to HCBD.

Renal damage as evidenced by renal tubular epithelial degeneration, necrosis, and an increase in the kidney weight:body weight ratio occurred in female rats receiving 30, 65, or 100 mg/kg/day HCBD for 30 days in their diet (Kociba, et al. 1971). No histopathological changes were observed at the 3 mg/kg/day HCBD dosage level. Other effects observed were decreased food consumption and decreased body weight gains for female rats consuming 10, 30, 65, and 100 mg/kg/day HCBD in their diet; depletion of abdominal fat - 65 and 100 mg/kg/day; minimal hepatocellular swelling - 100 mg/kg/day; and hemoconcentration - 10, 30, 65, and 100 mg/kg.

Dietary ingestion of 20 but not 2.0 and 0.2 mg/kg/day HCBD for 2 years

caused depression of the body weight gain of both male and female rats (Kociba, et al. 1977). Evaluation of the mean organ weights and organ: body weight ratio for rats killed at the termination of this study indicated the males had no alterations in weights of the brain, heart, and liver relative to control values. The relative and absolute weight of the kidneys of males ingesting the 20 mg/kg/day were statistically increased. For females, the body weight loss was accompanied by a significant decrease in the absolute weight of the heart and liver, and an increase in the relative weight of the kidney. A decreased survival rate was observed for males but not for females at 20 mg/kg/day HCBD.

Extensive gross and microscopic pathological examination of all rats necropsied during the course of this study was conducted. Significant abnormalities were observed in the urinary systems of rats receiving the 20 mg/kg/day dosage level. Among effects related to HCBD treatment was an increase over the controls in renal tubular neoplasms in both male and female rats. The effects at 2 mg/kg/day HCBD were slight, including possible renal tubular epithelial hyperplasia. No effects were observed in rats receiving 0.2 mg/kg/day HCBD in their diet for 2 years.

Blood, serum, and urine samples were analyzed for a wide variety of clinical indicators. A statistically significant increase in urinary coproporphyrin was observed in male rats ingesting 20 mg/kg/day HCBD for 12 months, in females ingesting 2.0 mg/kg/day for 14 months, and in females ingesting 20 mg/kg/day HCBD for 24 months.

A study of the effects of HCBD on reproduction in rats included gross and microscopic examination of internal organs, bone, and other tissues (Schwetz, et al. 1977). Pathological changes considered to be related to ingestion of HCBD were found in the kidneys of both male and female rats at dietary dose levels of 2 and 20 mg/kg/day HCBD for 148 days. Kidneys from male rats at these two dose levels were "roughened" and had a mottled cortex. There was renal tubular dilation and hypertrophy with foci of renal tubular epithelial degeneration and regeneration in kidneys from male and female rats on 20 mg/kg/day HCBD. No effects were observed at 0.2 mg/kg/day.

An effect on the central nervous system was observed at a 7 mg/kg dose level as a reduction in the ability of the rat to form conditioned reflex connections (Murzakaev, 1967). Results at 0.04 mg/kg were not statistically significant, while 0.004 mg/kg HCBD gave no indication of a neurotoxic response. Poteryaeva (1973) measured urinary acid-base equilibrium, serum peroxidase, residual N, and neuromuscular chronaxy in rats receiving daily oral doses of HCBD. HCBD toxicity was observed at 0.02 mg/kg/day for 1 month, at 0.004 mg/kg/day for 4 months, and threshold toxicity at 0.0005 mg/kg/day after 6 months.

Kidney damage is also induced by inhalation of HCBD. Fifteen daily 6-hour exposures of rats of 25 ppm HCBD caused respiratory difficulty, decreased weight gain, and pathologic injury to the tubular epithelium of the kidneys. Twelve daily 6-hour exposures to 100 ppm HCBD caused more severe toxicity, including the death of some rats. Fifteen daily 6-hour exposures to 10 or 5 ppm HCBD caused no toxicity except for retarded weight gain in females exposed to 10 ppm (Gage, 1970).

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Chernokan (1970) determined the dermal LD_{50} of HCBD for the rat at 4,330 mg/kg. Animals receiving 1/5 dermal LD_{50} showed general weight loss, sluggishness, and paresis of the extremities within 1 day of the start of the experiment, and all had died by the fifth to sixth day. With repeated applications of 1/20 dermal LD_{50} HCBD, features of intoxication began showing up by the sixth day which were expressed in weight loss, flaccidity, and rigidity of muscles. The red blood cell was the most sensitive initial indicator of toxicity as manifested by a loss in hemoglobin level and a drop in erythrocyte count.

Boranova (1974) observed that oral administration of 1 mg/day HCBD to puppies from birth to 6 months increased excretion of total N containing compounds and of urea N starting on the 20th day of growth. Total acidity of gastric juices and content of free HCl also were increased. A single dose of 60 or 90 mg/kg to guinea pigs caused decompensatory acidosis which was most significant at 5 days (Popovich, 1975). Blood indicators of acid base equilibrium and urine indicators tended toward normalization at 15 days.

The kidney appears to be the organ most sensitive to HCBD. Possible chronic effects are observed at doses as low as 2 to 3 mg/kg/day (Kociba, et al. 1971, 1977; Schwetz, et al. 1977). Renal tubular neoplasms were observed during a 2-year study in which 20 mg/kg/day was administered to rats in their diet (Kociba, et al. 1977). Single oral doses as low as 8.4 mg/kg have been observed to have a deleterious effect on the kidney (Shroit, 1972). Neurotoxic effects have been reported at even lower dose levels (Poteryaeva, 1973; Murzakaev, 1967), but these are difficult to quantify. Acute HCBD intoxication affects acid-based equilibrium in blood and urine

(Popovich, 1975; Poteryaeva, 1971). Some investigators report a cumulative effect for HCBD during chronic dosing by dermal (Chernokan, 1970) or oral Poteryaeva, 1973) routes. An increase in urinary coproporphyrin was observed in rats receiving 2 mg/kg/day and 20 mg/kg/day HCBD for up to 24 months (Kociba, 1977).

In Russia where HCBD is used as a soil fumigant for grape phylloxera, exposure of vineyard workers has occurred. Measurements showed that HCBD persisted in the air at levels from 0.0012 to 0.01 mg/liter for up to 5 days depending upon weather, application method, and soil tillage (Krasniuk, 1969). A medical examination was done of 205 workers, 153 with 4 years' exposure to HCBD and polychlorobutane-80 (a mixture of lower chlorine substituted isomers of 1,3 butadiene) and 52 working under the same conditions but with no exposure to these compounds. Arterial hypotension, as a rule, was noted in HCBD and polychlorobutane-80 exposed persons. Heart changes, including myocardial dystrophy, were found more frequently in workers in contact with the fumigant than in workers with no contact. Dyspeptic signs and periodic epigastric pains with food intake were observed in 38. Nervous disorders and upper respiratory tract changes occurred more frequently in exposed than in nonexposed workers. Details and statistical significance tests of the findings are lacking.

McConnell, et al. (1975) reported finding HCBD in human liver samples in the range of 12 µg/kg wet tissue and in body fat at around 4 µg/kg.

B. Synergistic or Antagonistic Compounds

Murzakaev (1967) found a decreased -SH group content in the cerebral cortex homogenate and blood serum of rats receiving a 7 mg/kg parenteral dose of HCBD over a 6-month span (frequency of dose not given). Mizyukova (1973) determined the relationship between the structure and detoxifying power of thiols and amines against HCBD. Rats poisoned with 300 mg/kg or larger doses of HCBD were given thiols or amines 20 to 30 minutes before and immediately after poisoning. The antidotes were administered orally in two-fold molar excess relative to the poison. As determined from the survival rates, mercaptide, cysteine, and especially unithiol were highly effective antidoces for HCBD. The ethanolammonium salts of 2,3-dimercapto-propane sulfonic acid were even more powerful antidotes than unithiol, while the ethanolamines themselves, either alone or combined with unithiol, were ineffective. The reduction in free -SH groups following HCBD injection and the effective antidote with mercapto (-SH) compounds suggest that compounds containing mercapto groups have an antagonistic effect on HCBD.

C. Teratogenicity

Nonpregnant female rats were given single 20 mg/kg subcutaneous doses of HCBD (Poteryaeva, 1966). The course of the subsequent pregnancy and its outcome were followed. The pregnancy rate for the dosed rats was the same as in the control group. No stillbirths occurred, but all the offspring of the rats which had received HCBD died within 3 months of birth with 38 of 86 dying between days 1 and 28, and 48 of 86 dying between days 29 and 90. In the control group, 13 of 61 died within 14 days of birth with no deaths

occurring thereafter for up to 90 days. The weights of the young rats from the dosed mothers were markedly lower than the controls. At 2-1/2 months, when the rats showed marked toxic effects, gross pathologic changes were noted in the internal organs at autopsy. Damage to the kidney showed itself in the form of glomerulonaphritis. Blood smears showed degenerative changes in the red cells.

Schwetz, et al. (1977) studied the effects of a dietary dose of HCBD on reproduction in rats. Male and female rats were fed dose levels of 0.2, 2.0, or 20 mg/kg/day HCBD 90 days prior to mating, 15 days during mating, and subsequently throughout gestation and lactation. The toxic effects observed on these rats are given in Table 3 and Section III-A. Signs of toxicity observed among the adult rats at the two higher dose levels were decreased weight gain and food consumption, and alterations in the kidney structure in the form of a mottled cortex. The only effect on weanlings consisted of a slight decrease in body weight at 21 days of age at the 20 mg/kg/dose level. All parameters of the reproductive process including neonatal growth, survival, and development were normal at levels of 0.2 or 2.0 mg/kg/day.

The discrepancy between the survival rates and observations on young rats reported by Schwetz (1977) and Poteryaeva (1966) suggests the need for more research on the teratogenic effects of HCBD. The difference in routes of administration and absorption may account for differences in survival rates and toxic effects. Also, Schwetz (1977) reports a 94 percent survival rate for newborn controls up to day 14, whereas Poteryaeva (1966) reports only a 79 percent survival rate for controls.

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A study published by Schwetz, et al. (1974) dealt with the effects of HCBD on reproduction in Japanese quail. Adult male and female Japanese quail were fed diets containing 0.2, 3, 10, or 30 mg/kg of HCBD for 90 days. The birds showed no evident signs of toxicity during the study. HCBD at all dose levels had no effect on body weight, demeanor, food consumption, egg production, the percent fertility and hatchability of eggs, the survival of hatched chicks, and eggshell thickness. In addition, at the termination of the study there were no gross or histopathologic changes evident in the organs or tissues of birds which could be related to treatment.

D. Mutagenicity

Taylor (1978) has tested the mutagenic potential of HCBD on S. typhimurium TA100. A dose dependent increase in reversion rate in the absence of activation was observed, but the usual criterion for mutagenicity of double the background rate was not reached. Solubility of HCBD in the test system was a problem and the final conclusion was classified as "not proven."

E. Carcinogenicity

Recently, Kociba, et al. (1977) completed a 2-year study of the chronic effects of HCBD in the rat. The results of the study are covered in Table 4 of this document. The most significant finding of these workers was the development of renal tubular neoplasms in the kidneys of rats receiving 20 mg/kg/day HCBD in their diet. Histological examination of the tumorous tissue revealed renal tubular adenomas and adenocarcinomas. Metastasis

TABLE 4. - (Kociba, et al. 1977)

Effects / Dose mg/kg/day	Numbers Male rat	% Response Male rat	Numbers Female rat	% Response Female rat	Observations
20.0	7/39	18	3/40	7.5	Renal tubular adenocarcinomas; undifferentiated carcinoma; metastasis to the lung
2.0	0/40	0	0/40	0	
0.2	0/40	0	0/40	0	
Control	1/90	1.1	1/90	1.1	Nephroblastoma

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to the lung was observed in two cases.

The HCBD was 99 percent pure. Test diets to supply 0, 20, 2, or 0.2 mg/kg/day were prepared weekly for the first 3 months of the study and monthly thereafter with concentrations of test material being adjusted to maintain the designated dosages on a mg/kg/day basis. Seven week-old male and female Sprague-Dawley (Spartan substrain) specific pathogen-free derived rats were used. They were housed in individual wire-bottom cages and food and water were accessible at all times. The rats were randomized into test groups of 39 to 40/sex/dose level plus 90/sex for controls.

In a previous unpublished 30-day toxicity study by this same laboratory (Kociba, et al. 1971), female rats received HCBD in doses ranging from 1 to 100 mg/kg/day. No effects were observed in rats receiving 3 mg/kg/day while effects were only marginal in rats receiving 10/mg/kg/day. The kidney was identified as the target organ. The no-effect levels observed are roughly in the same range as those reported by other investigators (Section III-A) and the kidney has been repeatedly identified as the target organ.

Feeding of the male rats continued for 22 months while the females were treated for 24 months. Gross and microscopic examinations were conducted on: (1) representative portions of all major organs; and (2) any tissue having a gross lesion suggestive of a significant pathological process taken from

rats killed in a moribund condition or dying during the course of the study. Terminal necropsy examinations were conducted on rats surviving the full term on the test diets. There was a significant increase in the mortality of the male rats ingesting 20 mg/kg/day HCBD during the last 2 months of the study. This was not the case with the males on the lower dose levels or in females at any dose level. Fifty percent of the high dose males had died by 18 months, while the survival rate for females was 21 to 22 months before a 50 percent death count was observed.

No significant increase in incidence of neoplastic lesions related to ingestion of HCBD was observed in any organ, tissue, or skeletal samples other than in the kidney. In the males receiving 20 mg/kg/day of HCBD, 18 percent (7/39) had renal tubular neoplasms which were classified as adenocarcinomas; 7.5 percent (3/40) of the females on the high dose developed renal carcinomas. Metastasis to the lung was observed in one case for both male and female rats. A nephroblastoma developed in one of the male control rats (1/90 or 1.1 percent) and in one of the female controls (1/90 of 1.1 percent). No carcinomas were observed in the kidneys of the control rats and no nephroblastomas were observed in the kidneys of the rats maintained on diets containing HCBD. Table 4 summarizes the data from Kociba, et al. (1977).

The production of lung adenomas in strain A mice following multiple IP injections of HCBD was investigated (Theiss, et al. 1977). Doses of 4 mg/kg and 8 mg/kg were administered IP (tricaprylin vehicle) three times a week to groups of 20 mice. Treatment continued until totals of 52 mg (4 mg/kg) and 96 mg (8 mg/kg) were administered. Twenty-four weeks after the first injec-

tion, the mice were killed. The frequency of lung tumors in HCBD treated rats was not statistically greater than in the vehicle-treated control group.

CRITERION FORMULATION

Existing Guidelines and Standards

There are no guidelines or standards of record other than a standard of 10 ug/m^3 for inhalation referenced by Poteryaeva, 1972, of the Soviet Union.

Current Levels of Human Risk

The analytical data available on the distribution of HCBD in the environment suggest that exposure is a localized problem, potentially affecting those living in areas with nearby chemical plants producing parent compounds for which HCBD is a by-product. However, due to the limited number of air and water samples taken, it is difficult to estimate the level of exposure even to those populations living in areas where the heaviest exposure might be encountered.

Special Groups at Risk

A special group at risk would be those workers in an industrial environment where concentrations of HCBD in the air might be present.

Basis and Derivation of Criterion

Hexachlorobutadiene (HCBD) exhibits acute, subacute and chronic toxicity in animal test systems, the overall data can be reviewed in Tables 2A, 2B, 3 and 4 (as presented in the document).

The kidney appears to be the organ most sensitive to HCBD. Chronic effects are observed at doses as low as 2 to 3 mg/kg/day in rats (Kociba, et al. 1971, 1977; Schwetz, et al. 1977). Renal tubular neoplasms were observed during a 2-year study in which 20 mg/kg/day was administered to rats in their

diet. Single oral doses as low as 8.4 mg/kg have been observed to have a deleterious effect on the kidney (Shroit, 1972).

The carcinogenic effects of renal tubular adenomas and adenocarcinomas were strongly demonstrated at the 20 mg/kg/day dosage. In addition, a dose-dependent increase in reversion rate was observed upon adding HCBD without activation to cultures of S. typhimurium. Although the observed rate was not quite double the background rate a mutagenic potential for HCBD is indicated (Taylor, 1978).

The evidence of carcinogencity is sufficient to conclude that HCBD is a suspect human carcinogen. As carcinogens are generally assumed to have a non-threshold dose/response characteristic, the carcinogenic effect is the most significant exposure effect from which to estimate an ambient water quality criterion value.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Hexachlorobutadiene is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of hexachlorobutadiene in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality

regulations, the concentrations of hexachlorobutadiene corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish. (2)	0	0.0077 µg/l	0.077 µg/l	0.77 µg/l
Consumption of fish and shellfish only.	0	0.0087 µg/l	0.087 µg/l	0.87 µg/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in the Methodology Document to the animal bioassay data presented in Appendix I and in Table 4. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Approximately 89 percent of the hexachlorobutadiene exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 870-fold. The remaining 11 percent of hexachlorobutadiene exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of hexachlorobutadiene, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding hexachlorobutadiene concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding hexachlorobutadiene concentrations. Because data indicating other sources of hexachlorobutadiene exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

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APPENDIX I

Derivation of Criterion for Hexachlorobutadiene

In the 2-year feeding study of Kociba (1977) in rats, renal tubular adenomas and carcinomas were observed in males with significantly higher incidence in animals fed 20 mg/kg/day (7/39) than control animals (1/90). Using a fish bioaccumulation factor of 870, the parameters of the extrapolation model are:

$n_t = 7$	le = 669 days
$N_t = 39$	d = 20 mg/kg/day
$n_c = 1$	w = 0.610 kg
$N_c = 90$	L = 730 days
Le = 730 days	R = 870

The result is that the water concentration should be less than 0.77 micrograms per liter in order to keep the individual lifetime risk below 10^{-5}.